Recent Probabilistic and Computational Advances in Dose-Response Assessment to Better Support Chemical Risk Assessment

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SRA/DRSG Webinar Series

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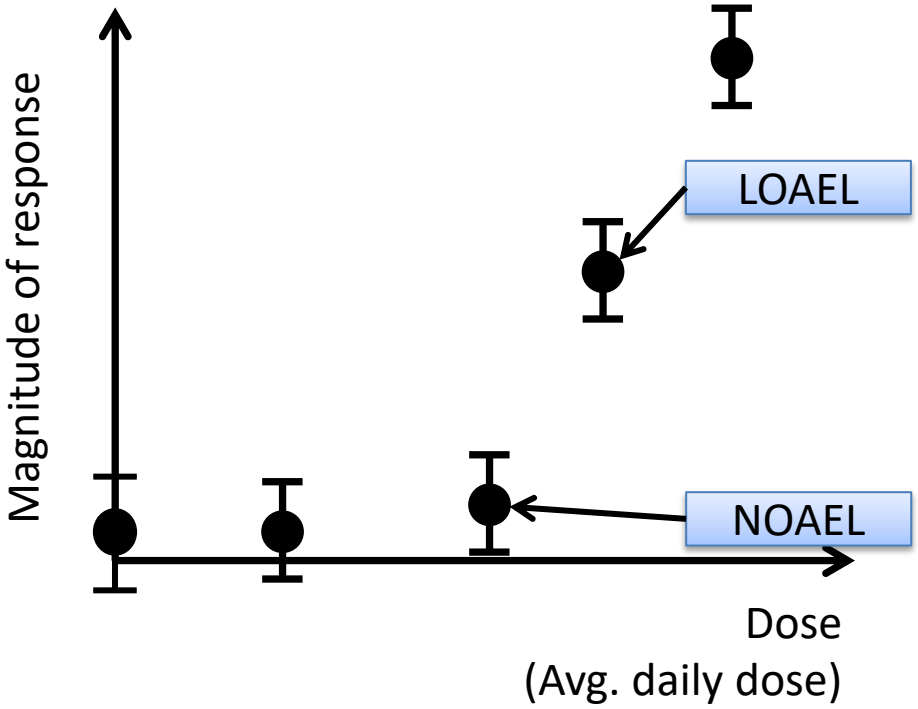
Outline

- Motivation and background
- Overview of the WHO/IPCS framework
- Recent advances in apply the WHO/IPCS framework
- Remaining challenges and summary

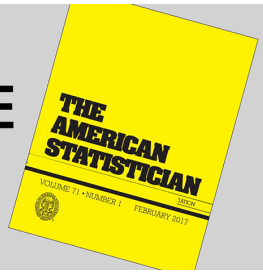
Limitations of the NOAEL

- Limited to doses in the study
- Minimum detectable response increases as sample size decreases
- Role of expert judgment often unclear
- Not comparable across studies
- Does not characterize uncertainty or variability



Concept of NOAEL based on statistical significance is ***fundamentally flawed***

SPECIAL ISSUE ON *P*-VALUE



Moving to a World Beyond "$p < 0.05$"

Ronald L. Wasserstein, Allen L. Schirm & Nicole A. Lazar

To cite this article: Ronald L. Wasserstein, Allen L. Schirm & Nicole A. Lazar (2019) Moving to a World Beyond "$p<0.05$", The American Statistician, 73:sup1, 1-19, DOI: 10.1080/00031305.2019.1583913

43 additional papers…

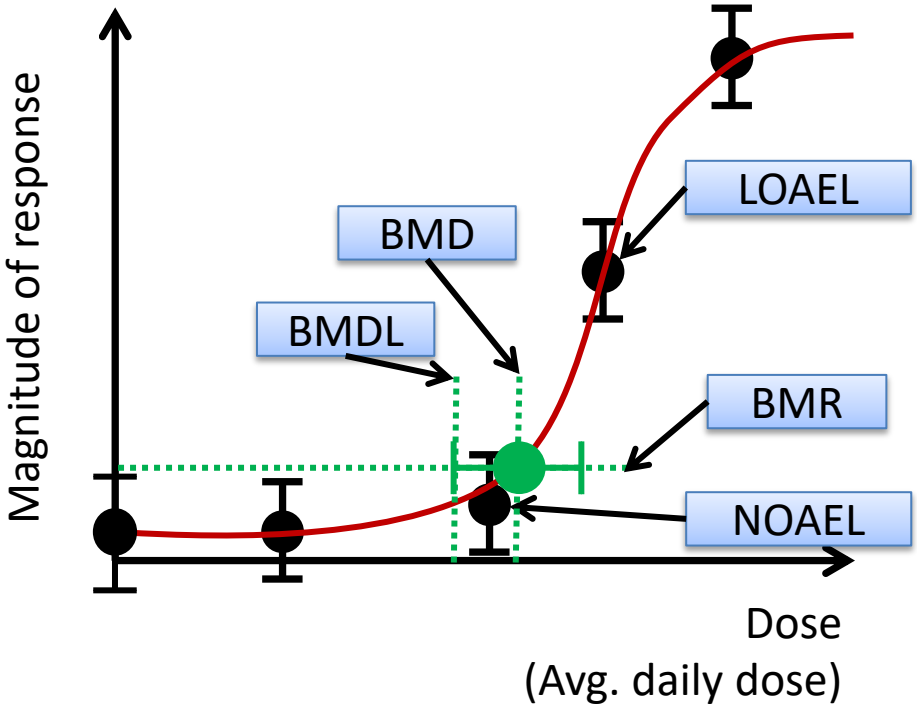
NOAEL, as practiced, violates ALL of these "don't"s

There's not much we can say here about the perils of *p*-values and significance testing that hasn't been said already for decades (Ziliak and McCloskey 2008; Hubbard 2016). If you're just arriving to the debate, here's a sampling of what not to do:

- Don't base your conclusions solely on whether an association or effect was found to be "statistically significant" (i.e., the *p*-value passed some arbitrary threshold such as $p < 0.05$).
- Don't believe that an association or effect exists just because it was statistically significant.
- Don't believe that an association or effect is absent just because it was not statistically significant.
- Don't believe that your *p*-value gives the probability that chance alone produced the observed association or effect or the probability that your test hypothesis is true.
- Don't conclude anything about scientific or practical importance based on statistical significance (or lack thereof).

Benefits of Benchmark Dose*

- Fitting a curve so not limited to doses in the study
- Magnitude of response fixed at a "benchmark response" (BMR) level
  - Clarifies role of expert judgment
  - Avoids misinterpretation as "threshold"
  - Aids comparability across studies
- **Accepts uncertainty,** and characterizes it in a confidence interval
  - Sample size
  - Experimental variability



*Crump (1984)

Benefits are a consequence of benchmark dose having a more precise definition than the NOAEL

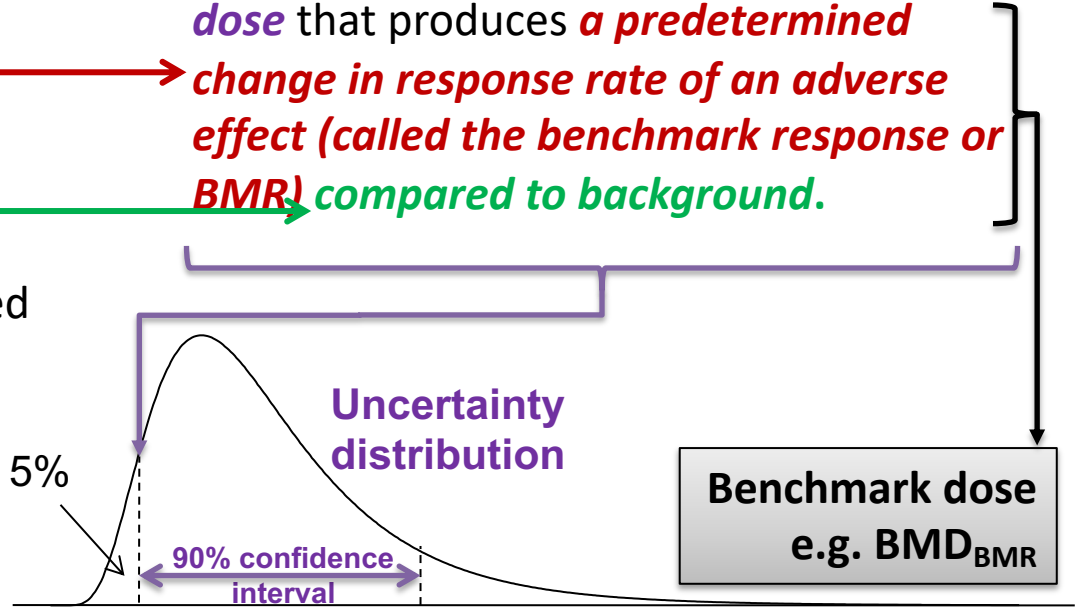
NOAEL:

Greatest concentration or amount of a substance, found by experiment or observation, that causes ***no adverse alteration …of the target organism distinguishable from those observed in normal (control) organisms*** of the same species and strain under the same defined conditions of exposure.

NOAEL should be viewed as an "approximation" of the BMD!

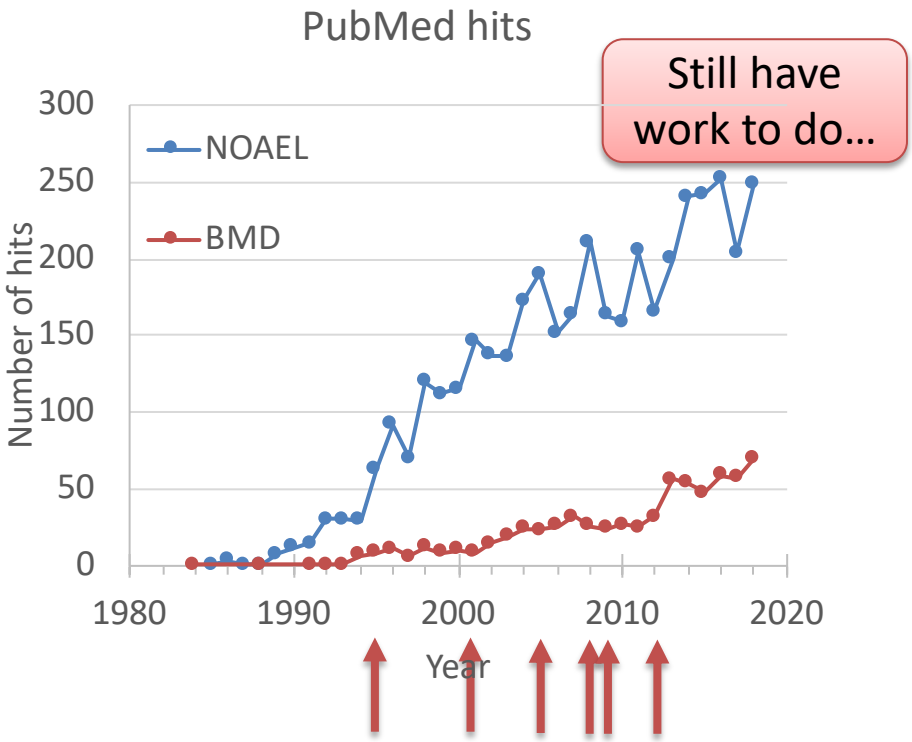
BMDL:

A statistical lower confidence limit on the dose that produces ***a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.***



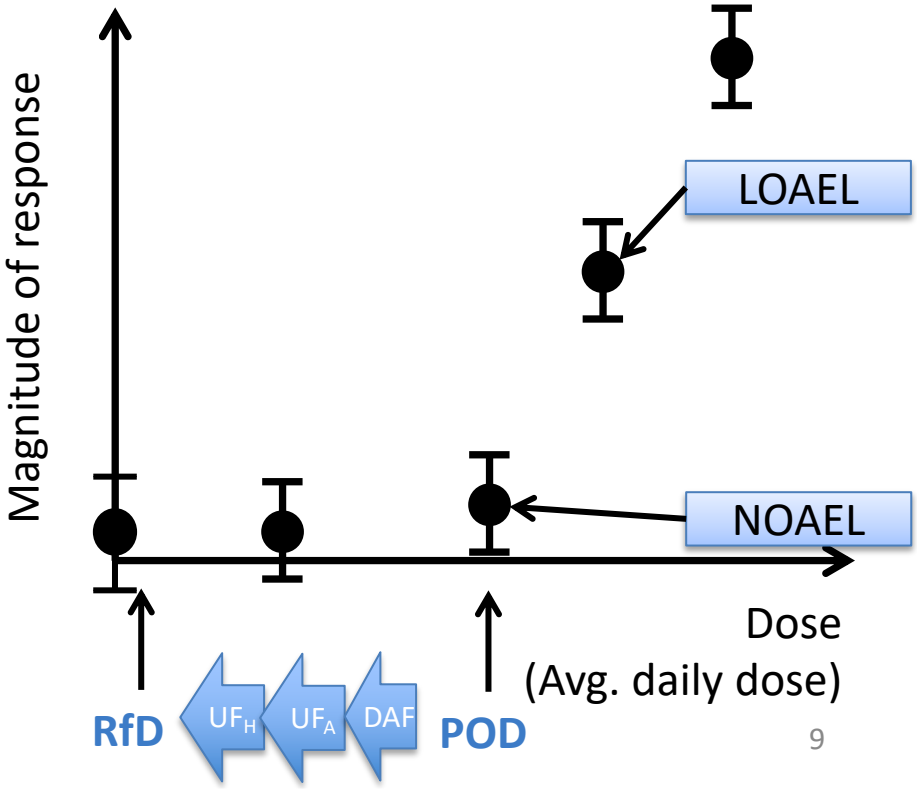
Generally Agreed that Benchmark Dose Is More Scientifically Valid than NOAEL

- U.S. EPA Risk Assessment Forum Report on The Use of the Benchmark Dose Approach in Health Risk Assessment (1995)
- National Research Council Standard Operating Procedures for Developing Acute Exposure Guideline Levels (2001)
- Joint FAO/WHO Meeting on Pesticide Residues (2005)
- European Chemicals Agency Guidance (2008)
- European Food Safety Authority Scientific Opinion (2009)
- World Health Organization Principles for modeling dose-response (2009)
- U.S. EPA Benchmark Dose Technical Guidance (2012)



Similar Issues with the deterministic RfD!

- **POD (Point of Departure):** If NOAEL, then ***magnitude of effect*** is unspecified and ***uncertainty*** is unquantified
- **DAF (Dosimetric Adjustment Factor):** Accounts for "average" interspecies differences (e.g., allometric scaling), uncertainty unquantified
- **UF_A (Interspecies Uncertainty Factor):** Assumed to be ***conservative***, but unclear by how much
- **UF_H (Intraspecies Uncertainty Factor):** Factor accounting for ***variability*** assumed to be ***conservative***, but unclear by how much and unspecified as to ***population fraction*** covered
- **RfD (Reference Dose):**
  - Assumed to be ***conservative***, but unclear by how much and unspecified as to ***population fraction*** covered
  - More ***conservative*** with more factors
  - Different assessments may differ greatly in level of ***conservatism***
  - Just providing a ***conservative*** bound not optimal for many types of decisions



Issues Recognized by the National Academies

- ***Science and Judgment*** report (NRC, 1994) recommended presenting quantitative representation of uncertainty.

- ***Science and Decisions*** report (NRC, 2009) recommended incorporating
  - Mode of action, vulnerable populations, background exposures
  - Unified approach to both cancer and non-cancer endpoints
  - Probabilistic methods for assessing uncertainty.

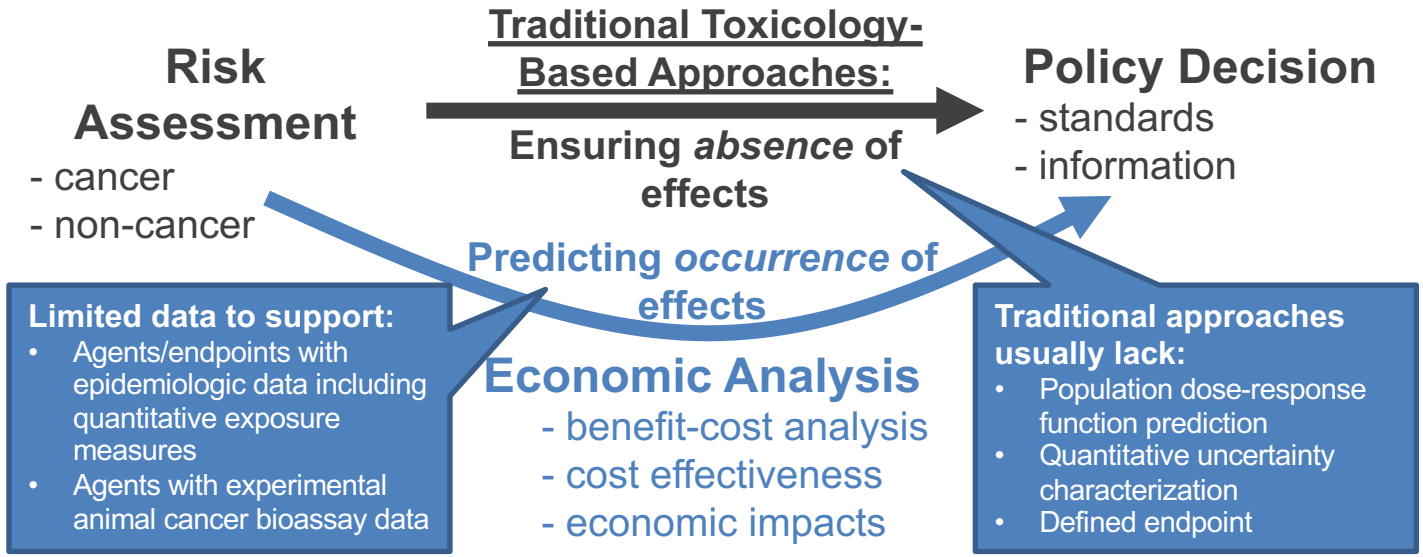
- ***Review of the IRIS Program*** report (NRC, 2014) recommended systematic use of uncertainty analysis and expanded use of Bayesian methods.

Existing RfD is ill-suited for many decision contexts

- Most chemical “risk assessments” are actually “safety assessments”
  - Risk: likelihood or probability of adverse effect(s)
  - Safety: providing “assurance” of an “absence” of risk

- Socio-economic benefits analyses require
  - Economically meaningful health effect(s)
  - Expected change in number of cases under different policy options

An Economist's View of Toxicology and Risk Assessment



Outline

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- **Overview of the WHO/IPCS framework**
- Recent advances in apply the WHO/IPCS framework
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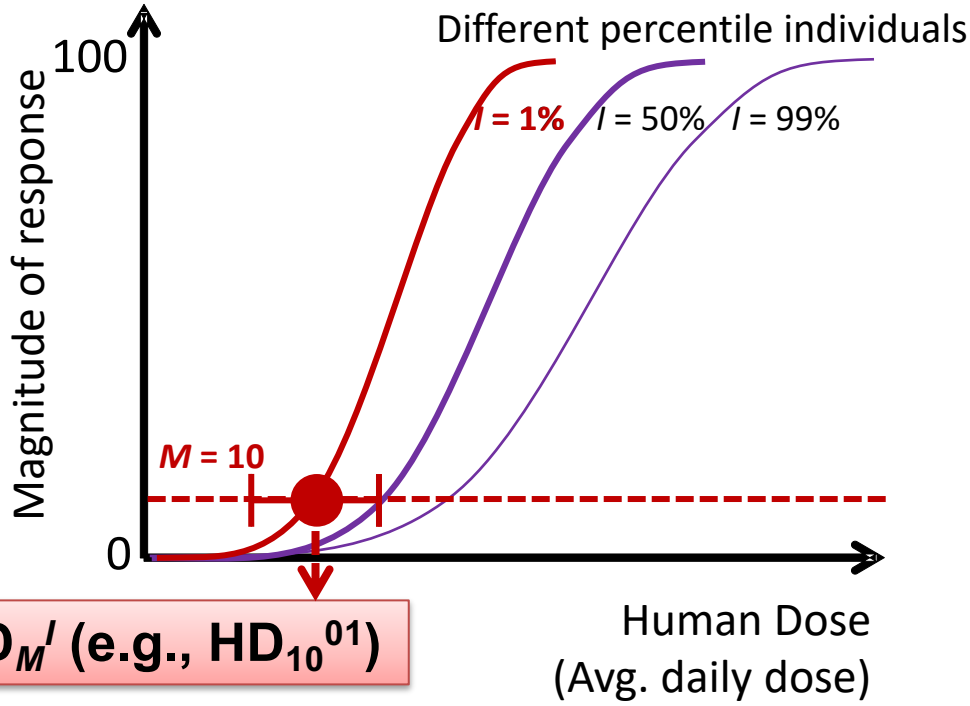
WHO approach to go “Beyond the RfD” to the “Target Human Dose”

- **Target Human Dose (HD_M^I):** human dose that at which a ***fraction I*** of the population shows an effect of ***magnitude (or severity) M*** or greater (for the critical effect considered).
- Specifies the “target” ***magnitude of effect M*** (analogous to BMR for the benchmark dose)
- Specifies “target” ***fraction of the variable population I (incidence)***
- Can be estimated probabilistically to derive a ***confidence interval*** that characterizes ***uncertainty***.



Key Concept: HD_M^I (e.g., HD_{10}^{01})

WHO (2014): Guidance on Evaluating and Expressing Uncertainty in Hazard Assessment. Harmonization Project Document 11.
Chiu WA & Slob W (2015): A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. EHP, DOI: 10.1289/ehp.1409385

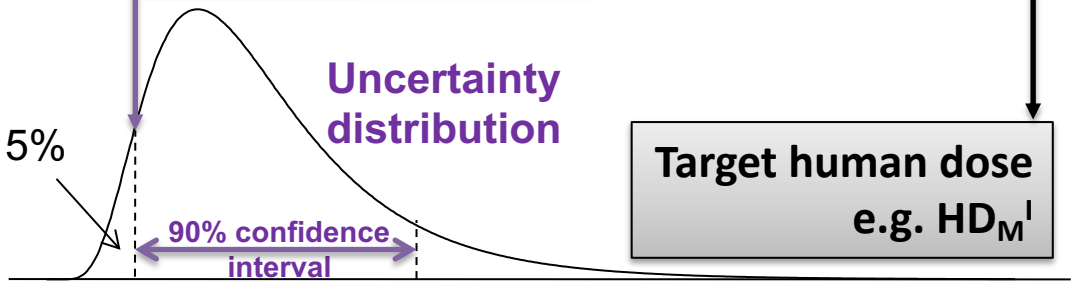
Target Human Dose (HD_M^I) and Probabilistic RfD have more precise definitions than the RfD

RfD:

An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the ***human population (including sensitive subgroups)*** that is ***likely*** to be ***without an appreciable risk*** of ***deleterious effects*** during a lifetime.

Probabilistic RfD:

A statistical lower confidence limit on the human dose that at which ***a fraction I of the population*** shows ***an effect of magnitude (or severity) M or greater (for the critical effect considered)***.



RfD should be viewed as an "approximation" of the HD_M^I!

Exactly analogous to transition from NOAEL to BMDL (*"déjà vu all over again…"*)

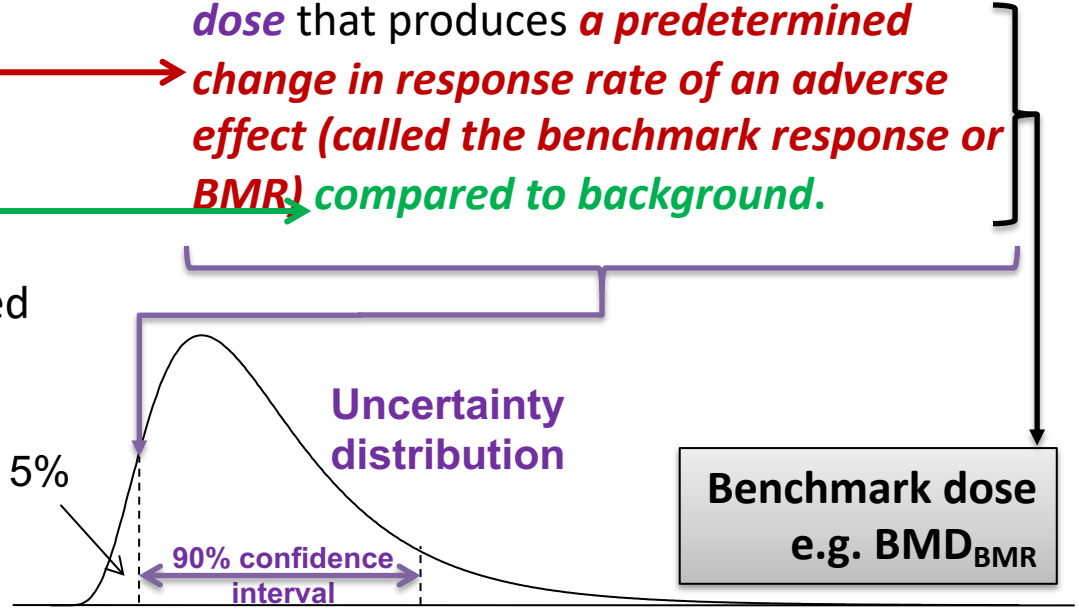
NOAEL:

Greatest concentration or amount of a substance, found by experiment or observation, that causes ***no adverse alteration …of the target organism distinguishable from those observed in normal (control) organisms*** of the same species and strain under the same defined conditions of exposure.

BMDL:

A statistical lower confidence limit on the dose that produces ***a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background.***

NOAEL should be viewed as an "approximation" of the BMD!

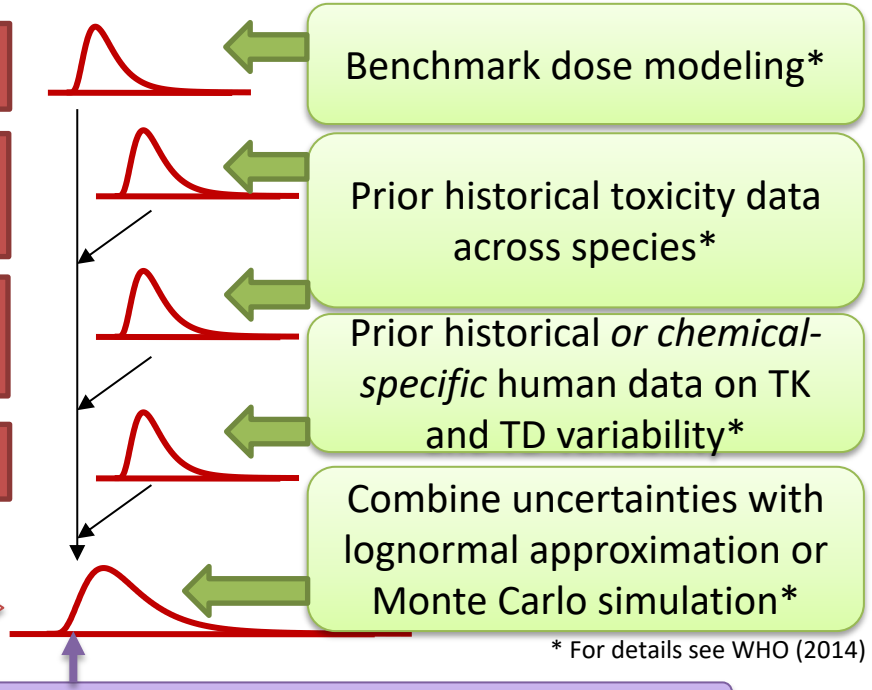


Target Human Dose Derived Similarly to a RfD, but Addressing Its Limitations

$$RfD = \frac{NOAEL \times DAF}{UF_A \times UF_H}$$

$$HD_M^I = \frac{BMD_M \times DAF}{UF_A \times UF_{H,I}}$$

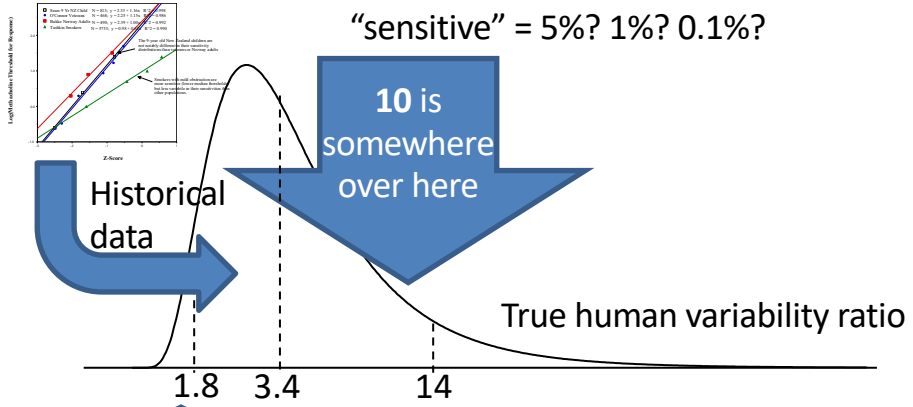
- Benchmark Dose for Magnitude of effect M
- Dosimetric Adjustment Factor for Body Size differences
- Interspecies Factor for remaining TK and TD differences
- Human Variability Factor for Incidence I



* For details see WHO (2014)

Lower Confidence Bound can be defined as a "Probabilistic RfD"

Revisiting "generic" uncertainty factors



(By definition of "sensitive," has to be >1)

Historical data on human variability:

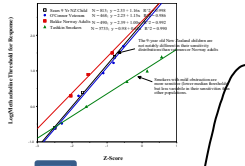
For "sensitive" = 5%

- Median ~ 3.4
- 95th %ile ~ 14
- 10 corresponds to ~90%ile

- What does a human variability factor of 10 mean?
  - The range from "least sensitive" to "most sensitive" humans is 10-fold.
  - "Sensitive" humans are 10x more sensitive than "typical" humans.
  - For most chemicals and endpoints, "sensitive" humans are no more than 10x more sensitive than "typical" humans.
- Thus, the TK and TD factors of 3 are intended to cover "most" chemicals for "sensitive" humans.

Reanalysis of Hattis and Lynch (2007) data by WHO/IPCS (2014).

Revisiting "generic" uncertainty factors



"most" = 90%? 95%? 99%?
"sensitive" = 5%? 1%? 0.1%?

10 is somewhere over here

Historical data

True human variability ratio

2.2 5.7 42

1.1 is somewhere over here

(By definition of "sensitive," has to be >1)

Historical data on human variability:

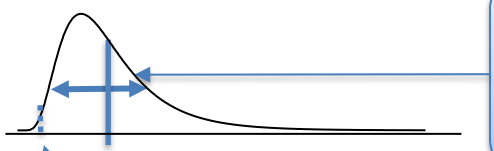
For "sensitive" = 1%

- Median ~ 5.7
- 95th %ile ~ 42
- 10 corresponds to ~70%ile

- What does a human variability factor of 10 mean?
  - The range from "least sensitive" to "most sensitive" humans is 10-fold.
  - "Sensitive" humans are 10x more sensitive than "typical" humans.
  - For most chemicals and endpoints, "sensitive" humans are no more than 10x more sensitive than "typical" humans.
- Thus, the TK and TD factors of 3 are intended to cover "most" chemicals for "sensitive" humans.

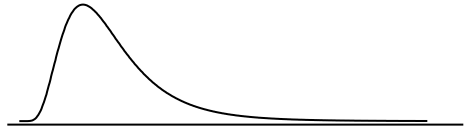
Reanalysis of Hattis and Lynch (2007) data by WHO/IPCS (2014).

Human variability: Disaggregating Uncertainty and Variability



Human equipotent dose

Variability distribution is approximately lognormal: **Interindividual variability, GSD_H**



Estimates of **Log(GSD_H)** for different chemicals

*l*th percentile defines "sensitive" individual being protected (e.g., 1st percentile)

$$UF_{Intra\text{-}l} = GSD_H^{|z_l|}$$

Uncertainty distribution is approximately lognormal: **Chemical-specific uncertainty, GSD_U**

Uncertainty distribution for $UF_{Intra\text{-}l}$

(depends on choice of *l*!)

Combining Uncertainties

APROBA & APROBAweb

- Uses lognormal distribution for each *factor*
- BMD approximated by lognormal with lower 5%ile=BMDL and either
  - median=BMD or
  - upper 95%ile=BMDU
- DAF & UF_A are already assumed to be lognormal
- $UF_{H,I} = GSD_H^{|z|}$ approximated by lognormal (equivalent to $\log(GSD_H)$ approximated by normal instead of being lognormal)
- Result is lognormal HD_M^I.

$$HD_M^I = \frac{BMD_M \times DAF}{UF_A \times UF_{H,I}}$$

Bayesian BMD

incorporates Chiu & Slob 2015 R code

- BMD distribution uses samples from Bayesian posterior
- Incorporates Chiu & Slob (2015) R code for MC simulation for remaining factors
- DAF & UF_A are sampled from their assumed lognormal distributions
- $UF_{H,I} = GSD_H^{|z|}$ samples drawn based on assumed lognormal distribution of $\log(GSD_H)$
- Result is set of samples for HD_M^I.

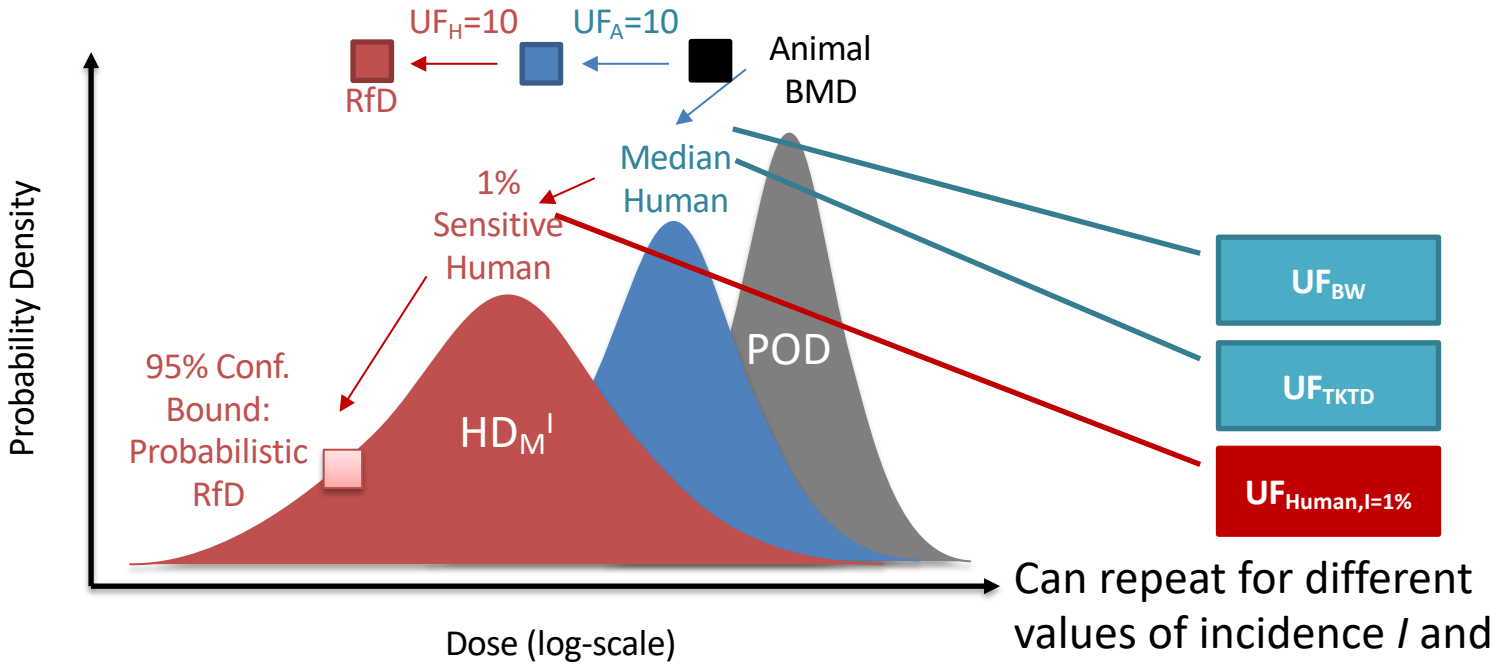
APROBAweb Interactive Web Application (based on Rshiny)
https://wchiu.shinyapps.io/APROBAweb/

Web-based Bayesian Benchmark Dose (BBMD) System
https://benchmarkdose.org/ (Shao & Shapiro 2018)

Illustration of HD_M^I Calculation

Probabilistic RfD:

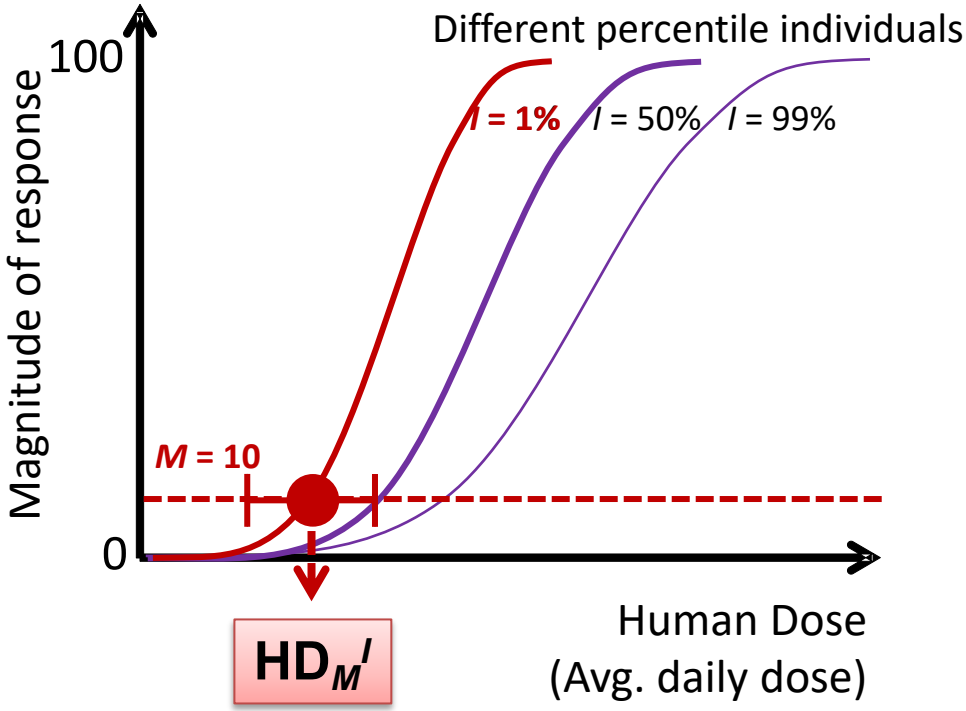
A statistical lower confidence limit on the human dose that at which ***a fraction I of the population*** shows ***an effect of magnitude (or severity) M or greater (for the critical effect considered)***.



Can repeat for different values of incidence *I* and magnitude *M*

Applications of Probabilistic Dose-Response

- Can **replace** RfD or RfC.
- Addresses **population variability** through ***I***.
- Provides a **dose-response function** through ***M***.
  - Effects of incremental changes in dose
  - Cumulative risk of multiple chemicals
- Characterizes **uncertainty**
- Can incorporate **chemical-specific data** on TK and TD variability



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Demonstration of Feasibility

- **Identification and curation of chemical RfDs**
  - Use only RfDs from federal health agencies
  - Wide range of effect types, PODs, composite UFs
- **Automated Workflow for Probabilistic dose-response assessment**
  - Convert to endpoint-specific RfDs
  - Assign conceptual models and uncertainty distributions
  - Combine uncertainties probabilistically

Demonstrating Feasibility

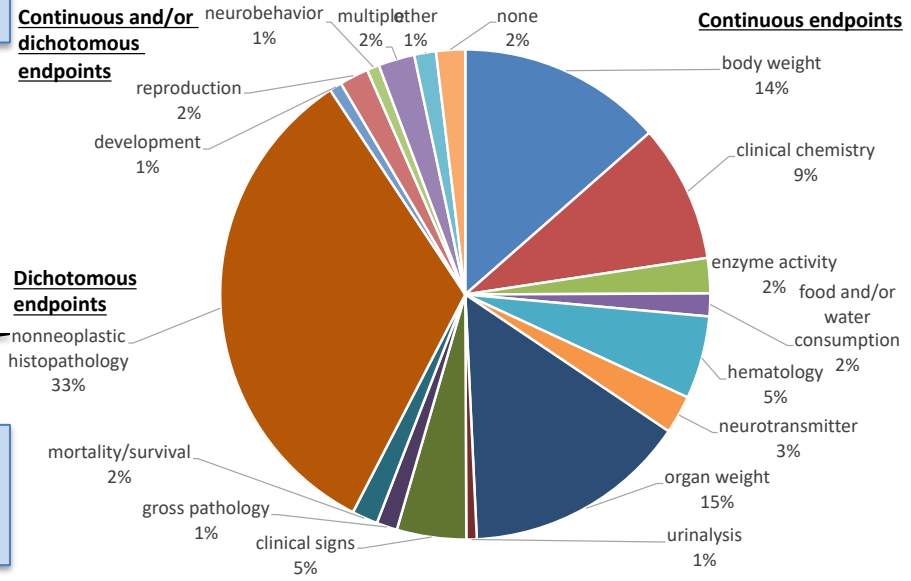
3064 peer-reviewed toxicity values and endpoints from Wignall et al. (2014)

- Non-cancer, oral RfDs
- Based on animal data
- Sufficient reporting of species, points of departure, uncertainty factors, etc.

1464 RfDs and endpoints

608 Chemicals (351 with multiple RfDs or endpoints)

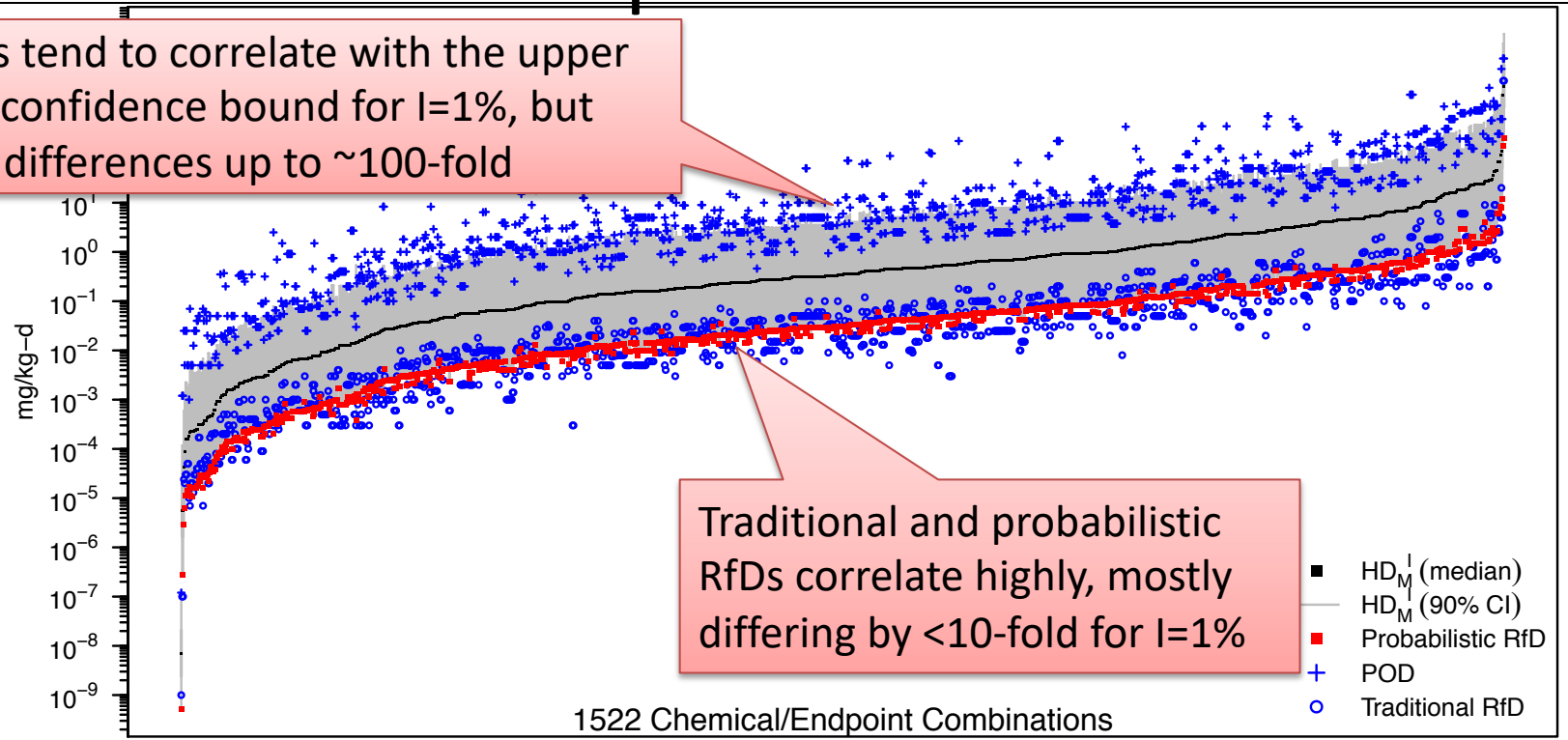
Effect Types



Re-Calculate using Probabilistic Methods

Comparing Traditional and Probabilistic Dose-Response Assessment

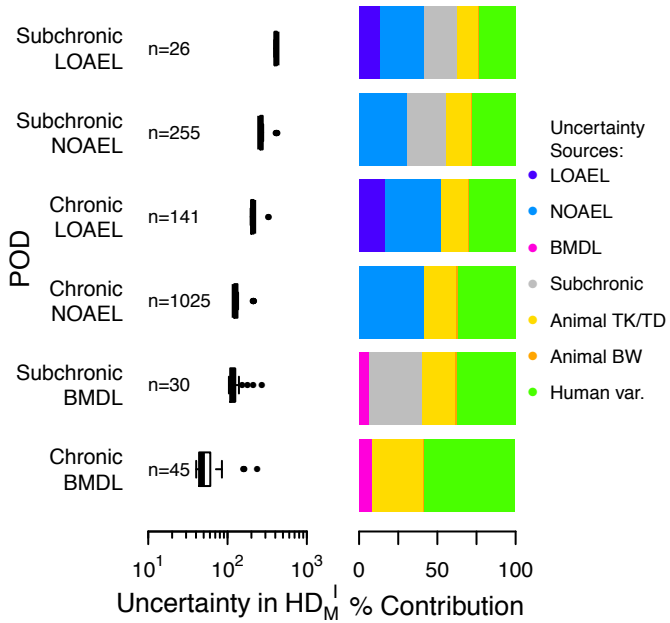
PODs tend to correlate with the upper 95% confidence bound for I=1%, but with differences up to ~100-fold



Traditional and probabilistic RfDs correlate highly, mostly differing by <10-fold for I=1%

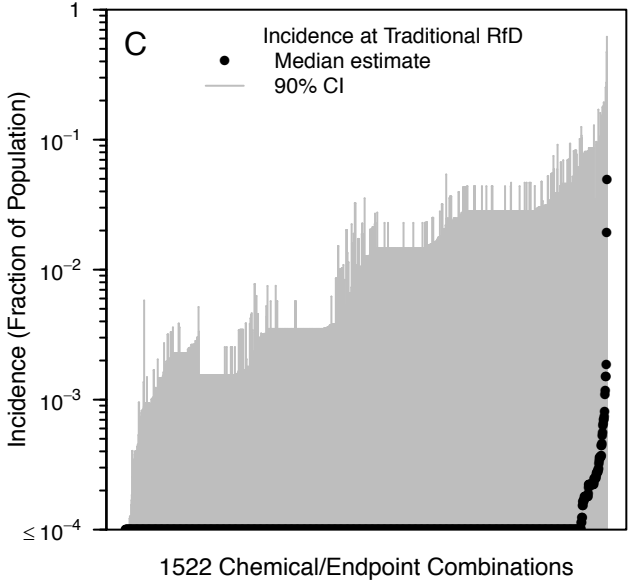
Sources of Uncertainty in HD_M^I

- Degree of uncertainty depends strongly on the POD type:
  - LOAELs from subchronic studies have greatest uncertainty (~400-fold range)
  - BMDLs from chronic studies have least uncertainty (~50-fold range).
  - Most common PODs were NOAELs from chronic studies (~100-fold range).
- Greatest contributors to uncertainty:
  - Lack of BMDL
  - Uncertainty about human variability



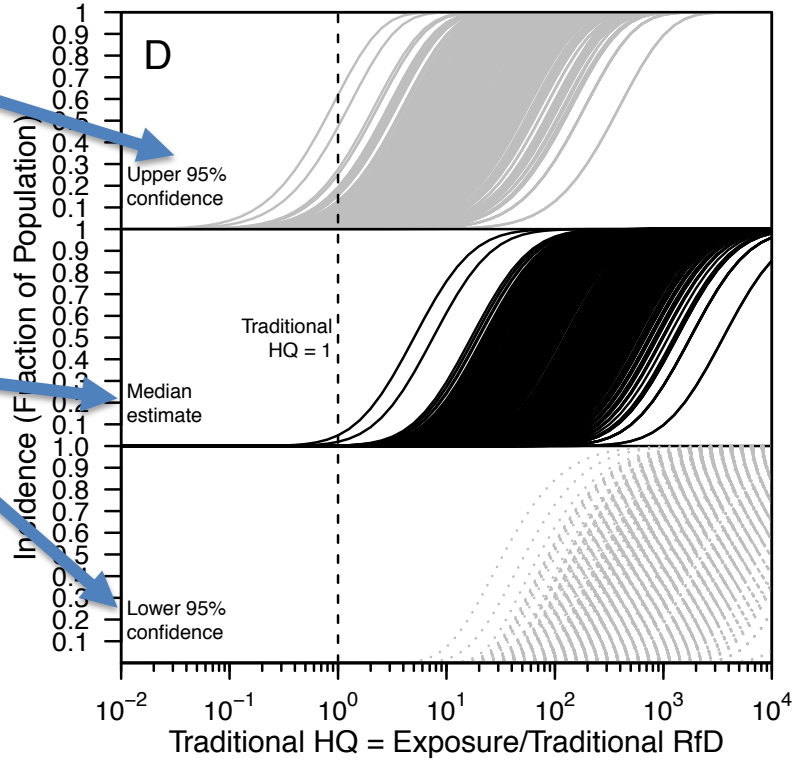
Residual Risk at Traditional RfD

- Upper bound risk typically a few percent
- Median and lower bound risks < 0.01%
- Severity of endpoints vary greatly (e.g., “mild irritation” vs. “hemorrhage”)



Generating Population Dose-Response Functions

- Upper bound risk at the traditional RfD is typically a few percent, but sometimes much more
- Median and lower bound risks mostly < 0.01%
- Can calculate expected values using Monte Carlo simulation



Chiu et al. (2018) https://doi.org/10.1289/EHP3368

Lessons Learned Across Many Chemicals and Endpoints

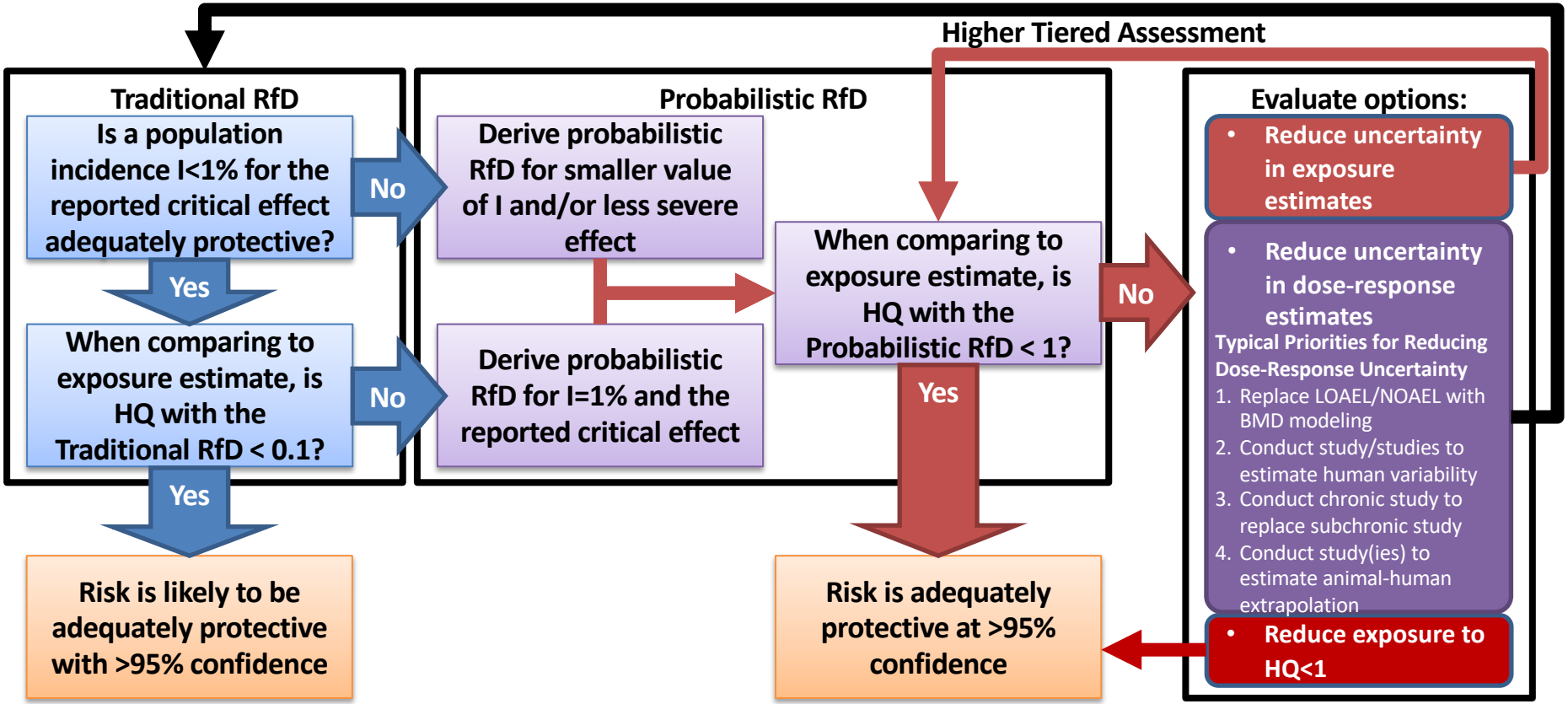
- **Broadly improving rigor, transparency, and consistency of dose-response assessment using probabilistic approach is feasible:**
  - Uncertainty factor distributions derived from historical evidence, not factors of 1, 3, or 10.
  - Combining uncertainty distributions probabilistically avoids "compounding conservatism."
  - The resulting HD_M^I is clear as to the degree of health protection (target incidence and magnitude of effect) and conservatism (% confidence)

- **Exposure at the current RfD**
  - Frequently implies upper 95% confidence bound incidence of a few percent
  - Whether such risks are "acceptable" may vary by context (including endpoint severity).

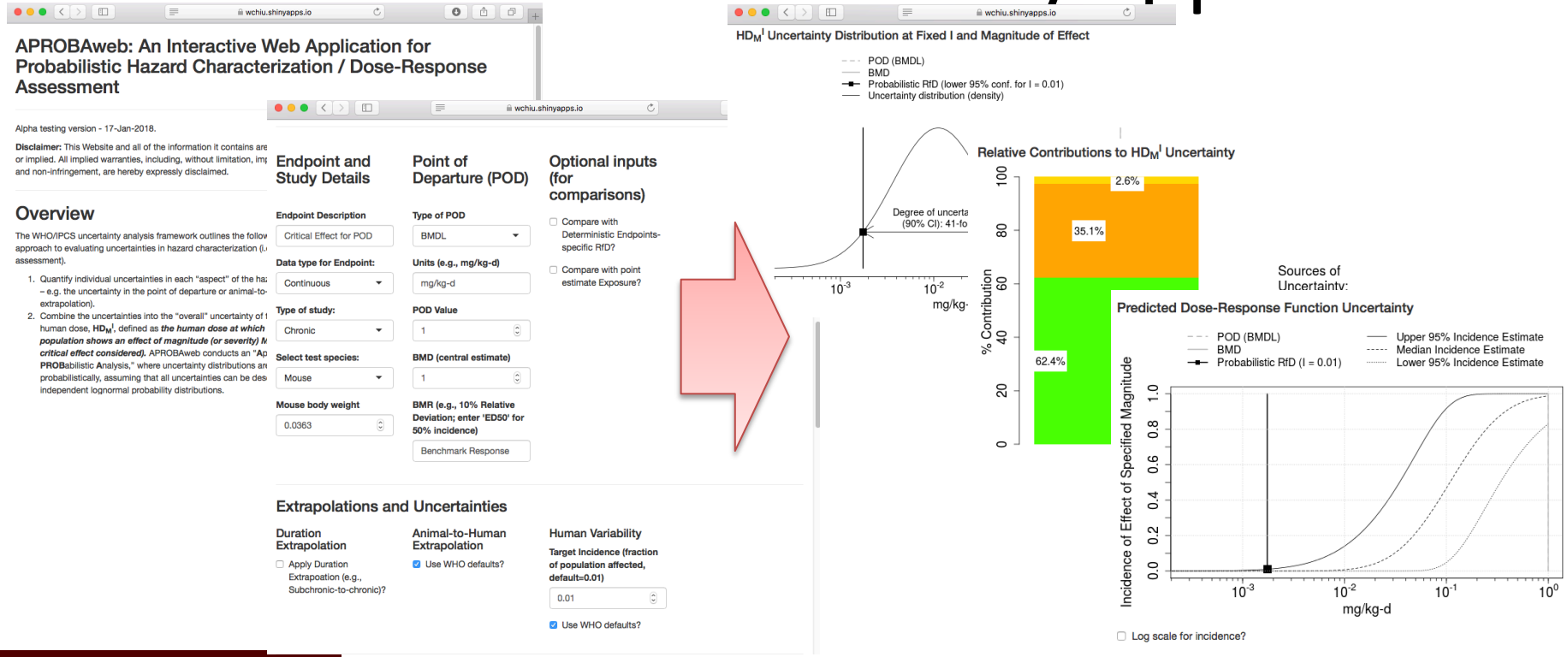
- **Broader use of BMD modeling can substantially reduce uncertainty.**

- **Research into the extent of human variability may warrant more emphasis than inter-species differences.**

Example Risk Assessment/Risk Management Workflow Incorporating Traditional RfD, Probabilistic RfD, and Tiered Uncertainty Reduction



Online Tools to Facilitate Computation: APROBAweb Rshiny app

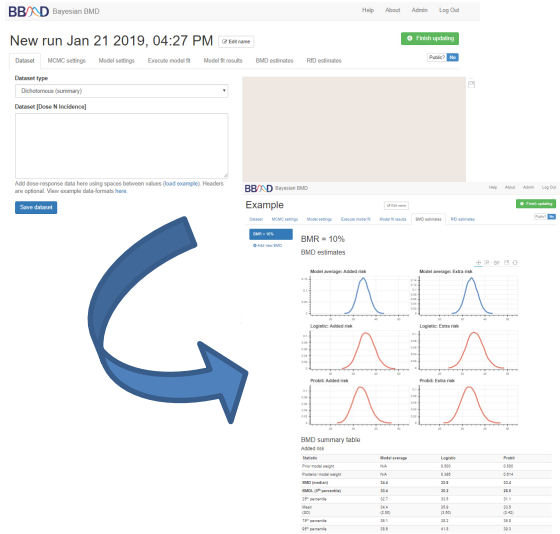


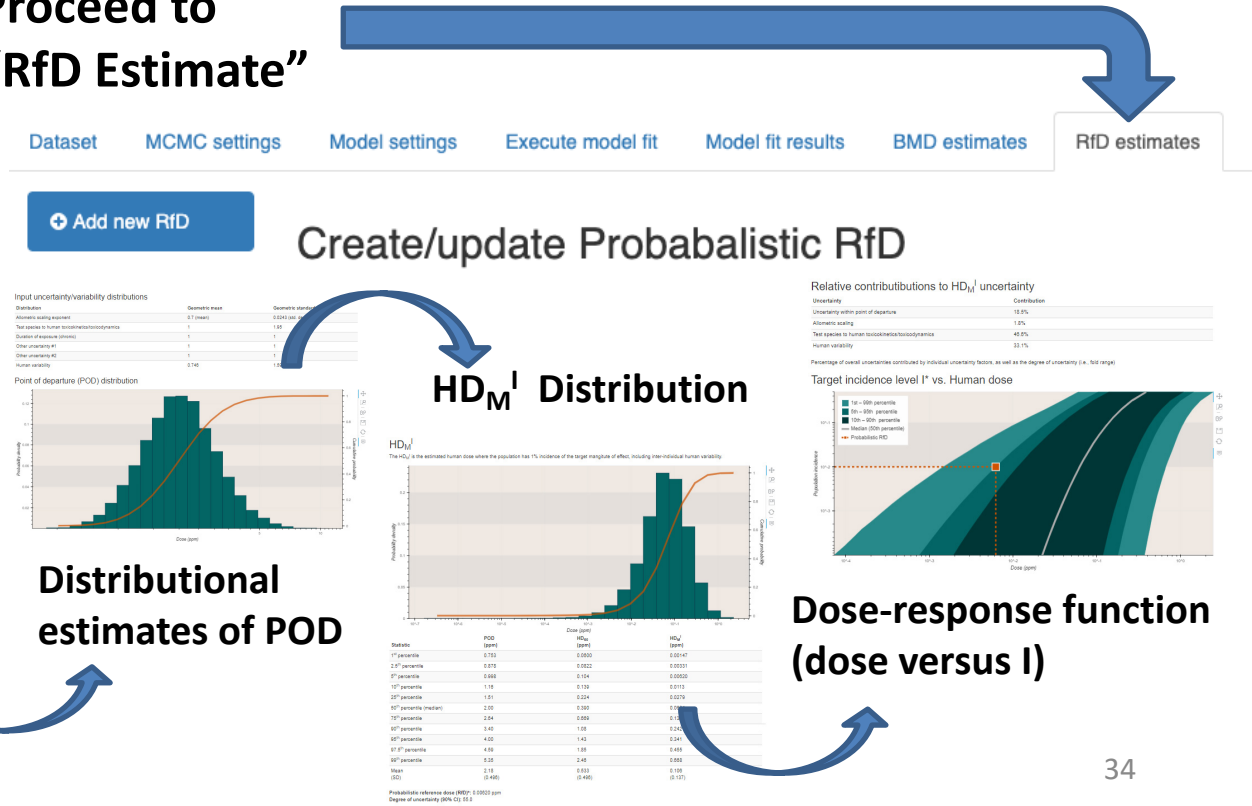
https://wchiu.shinyapps.io/APROBAweb/

Online Tools to Facilitate Computation: Bayesian Benchmark Dose Web Portal

BBMD analysis of datasets

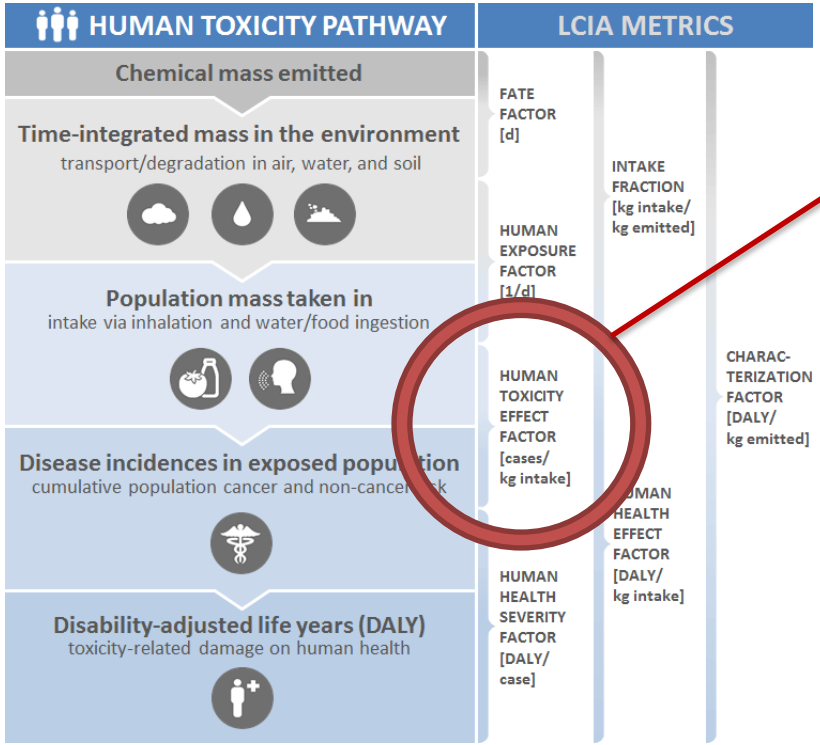
Proceed to "RfD Estimate"



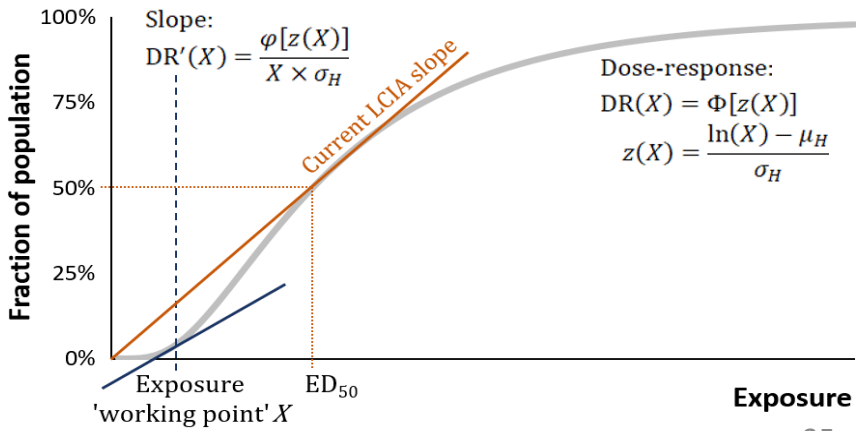


https://benchmarkdose.org/

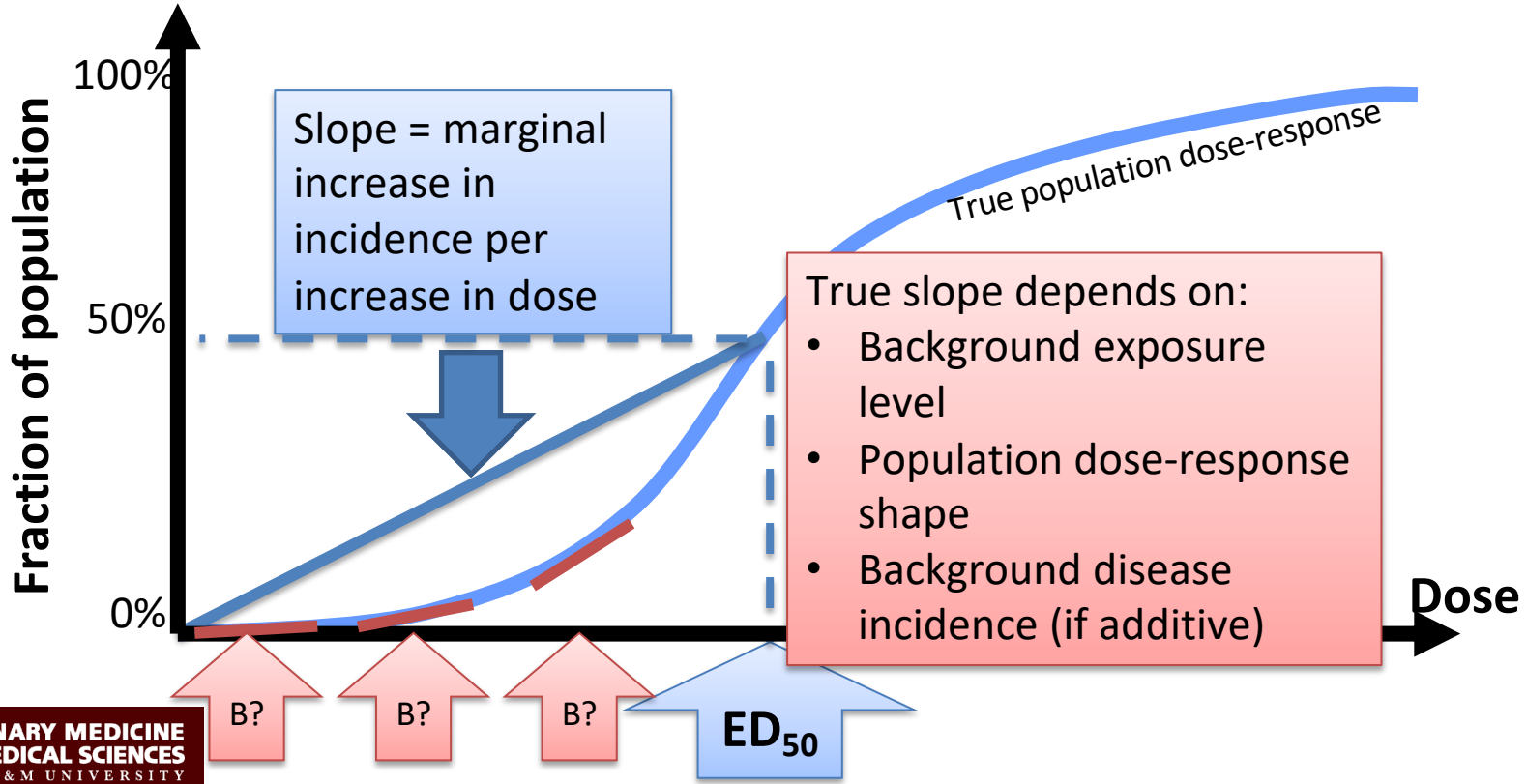
Application to Life-Cycle Impact Assessment



- Primarily used for *comparative risk assessments* of life-cycle impacts
- Requires *slope* of dose-response curve, not a "safe dose" level.



Current LCA Effect Factor (EF) based on linear extrapolation from ED_{50}

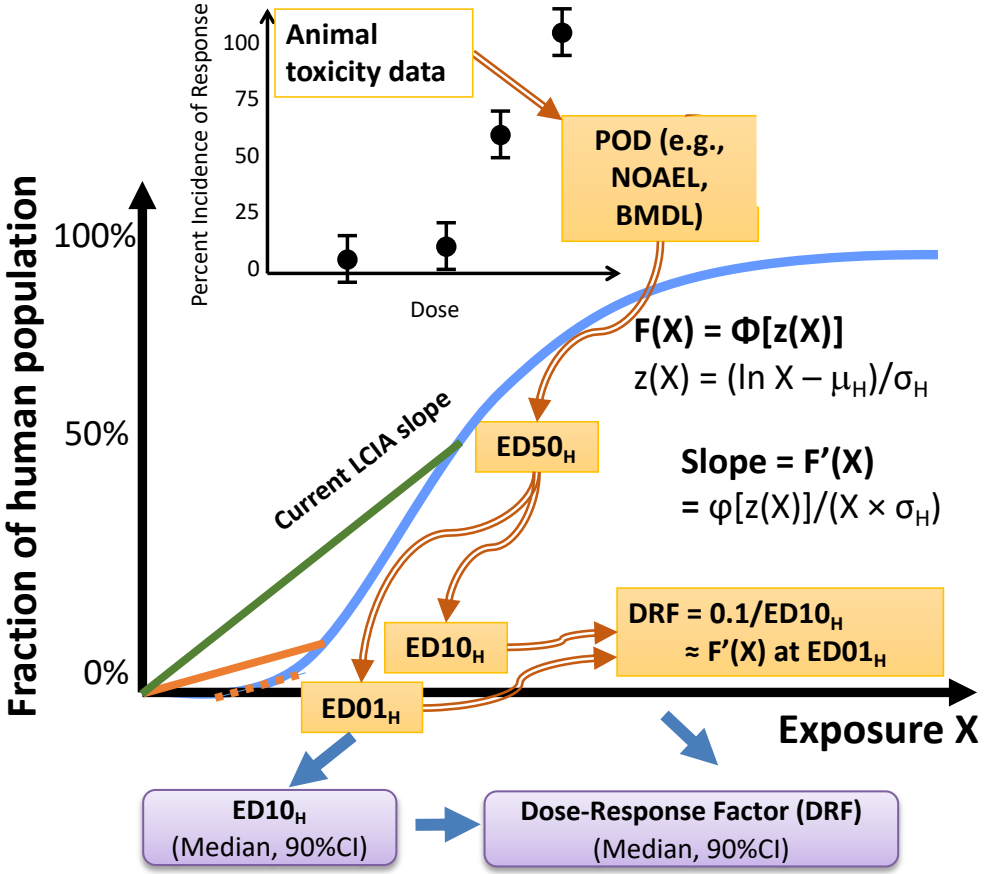


Proposed approach

- LCIA currently uses single point estimate for each factor
- *Linear slope* from the ED10 as a "reasonable" value (with 95% CI) for the *marginal slope* for a wide range of background exposures.
- Consistent with alternate interpretation that marginal slope should be at the background *disease incidence* due to additivity.

Challenges:

- LCIA analyses often include hundreds or thousands of chemicals simultaneously.
- Lack of regulatory toxicity values, or even any *in vivo* data, for vast majority of chemicals.

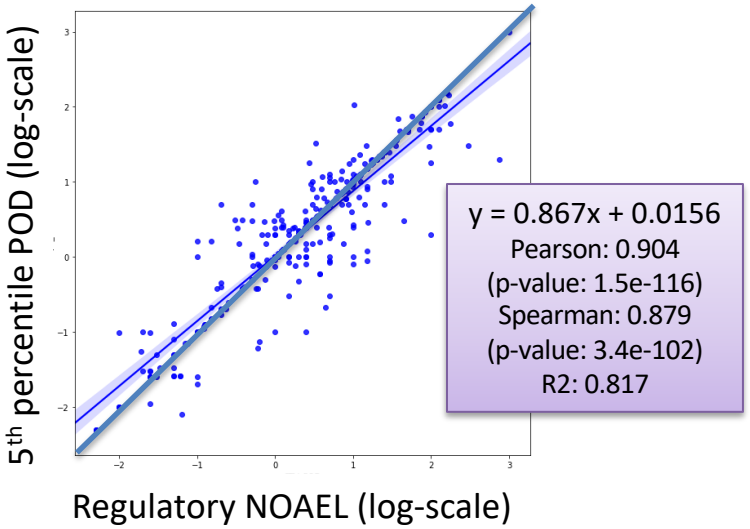


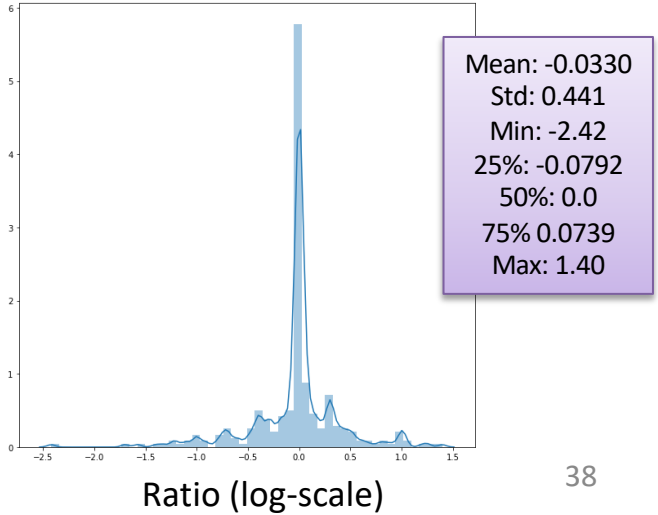
Experimental animal data: Regulatory vs. non-regulatory PODs

- Regulatory toxicity values undergo extensive review process for selecting in vivo PODs.

- In absence of regulatory values, which in vivo POD to use?
  - Minimum?
  - 5th percentile?
  - Median?

Unbiased, but with fat tails





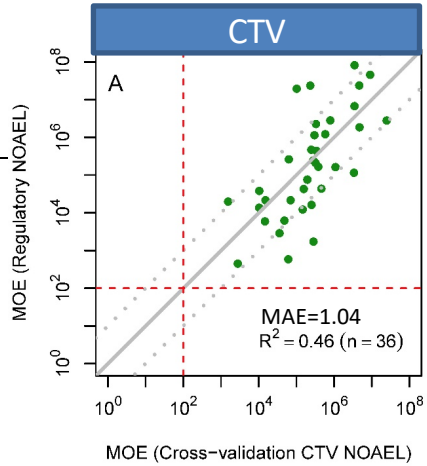
Data Sources: Paul Friedman et al. 2020; Wignall et al. 2018

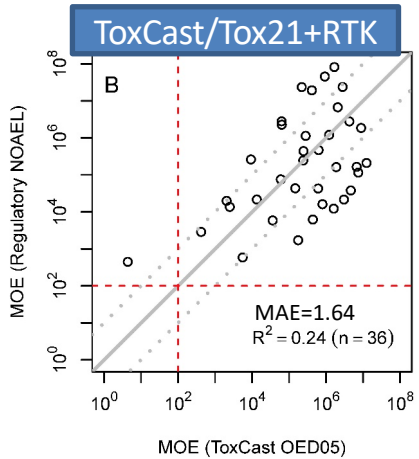
NAMs as PODs: QSAR vs. ToxCast/Tox21

- CTV (Wignall et al. 2018, toxvalue.org) developed a suite of QSAR models for predicting regulatory toxicity values (e.g., NOAELs) in the absence of *in vivo* data.
- ToxCast/Tox21 toxicity values for screening and prioritization based on
  - In vitro high throughput screen (HTS) assays
  - Reverse toxicokinetics (RTK) to convert in vitro concentrations to oral equivalent doses
- Can evaluate performance relative to "gold standard" of published regulatory toxicity values.

CTV (QSAR-based) has
- larger R^2 and
- smaller MAE

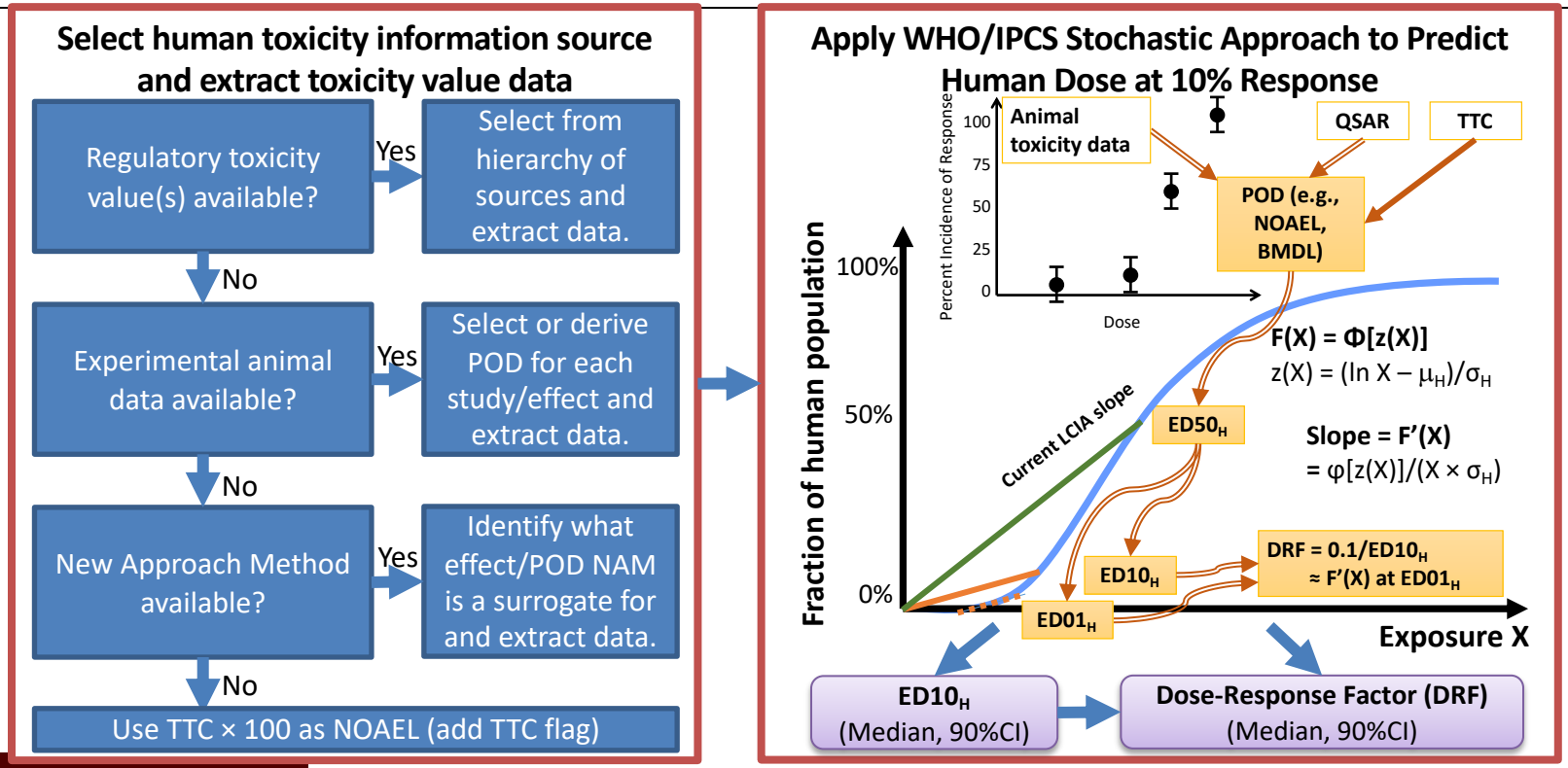
comparted to HTS+RTK-based OEDs



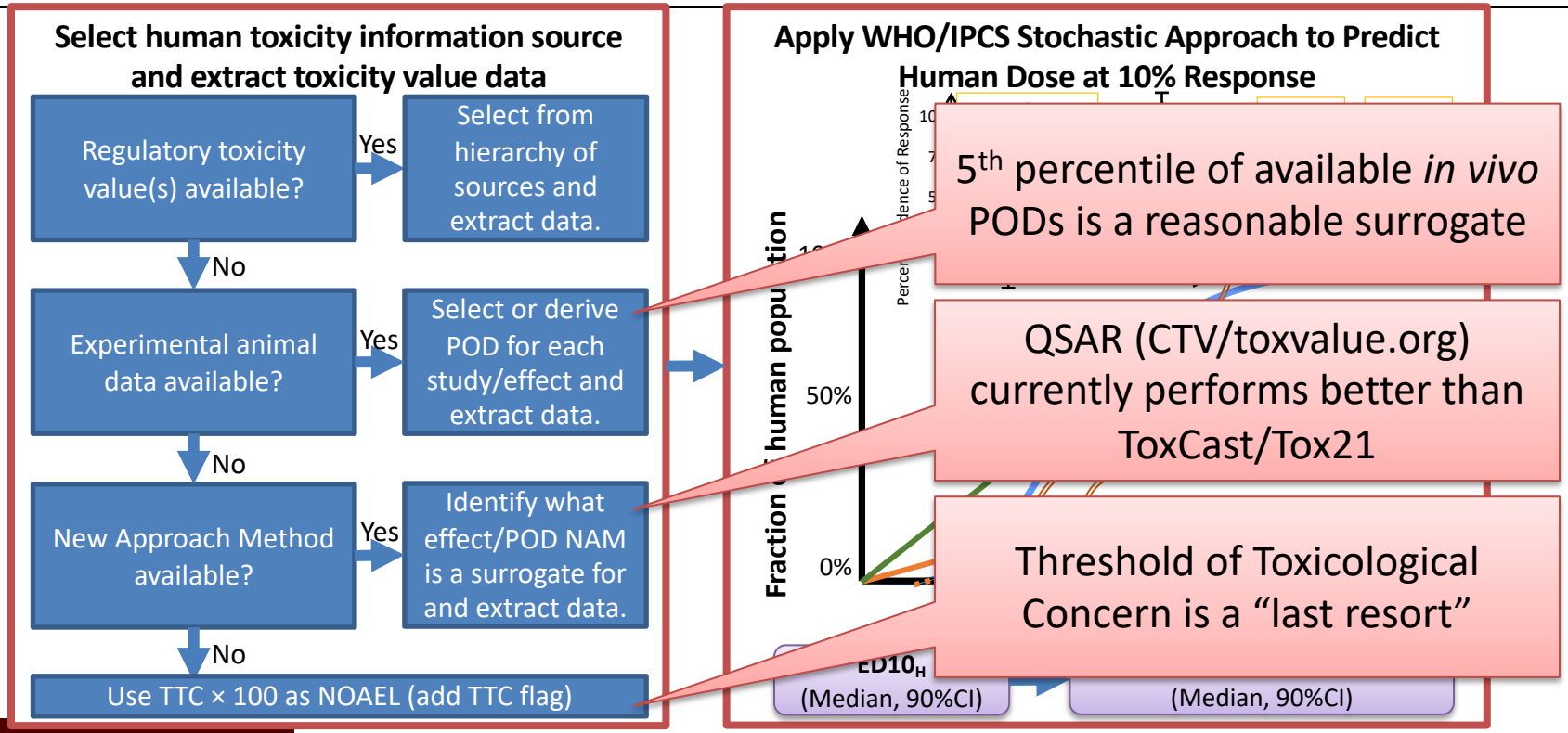


Source: Wignall et al. 2018

Proposed decision-tree flowchart



Proposed decision-tree flowchart



Analysis ongoing as part of UNEP / USETOX project…. Stay tuned!

Outline

- Motivation and background
- Overview of the WHO/IPCS framework
- Recent advances in apply the WHO/IPCS framework
- **Remaining challenges and summary**

Challenges ahead

- Quantification challenges
  - Even animal toxicology data is limited to at most a few thousand chemicals/endpoints – more investigation of use of NAMs needed
  - For benefit-cost analyses, difficulty in assigning economic value to most toxicology endpoints
  - High uncertainty for low levels of incidence

- Institutional and communication challenges
  - Lack of experience/training with probabilistic methods
  - Requires more explicit risk management specification of protection goals (no longer binary)
  - Communicating residual risk & uncertainty is difficult.

Summary

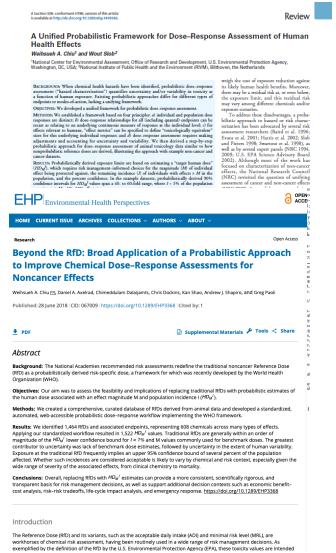
Bottom line: WHO/IPCS probabilistic approaches provides a substantial bridge between toxicology data and a broader suite of risk management decision contexts.

- Replacing RfD with HD_M^I is directly analogous to replacing the NOAEL with the BMDL.
- Approach addresses numerous limitations of current practices.
- Results include point estimates, confidence limits, and continuous dose-response functions.
- Framework can be broadly implemented using existing software and tools.
- Numerous opportunities exist beyond economic benefits analysis for employing more useful dose-response assessments
- Several challenges remain for broader application.

For more information…

Publications

- WHO (2014, 2017 [2nd edition]): Guidance on Evaluating and Expressing Uncertainty in Hazard Assessment. http://www.who.int/ipcs/methods/harmonization/areas/hazard_assessment/en/ (including APROBA spreadsheet)
- Bokkers et al. (2017) APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances.. FCT, DOI: https://doi.org/10.1016/j.fct.2017.10.038
- Chiu WA & Slob W (2015): A Unified Probabilistic Framework for Dose-Response Assessment of Human Health Effects. EHP, DOI: http://dx.doi.org/10.1289/ehp.1409385
- Chiu WA. (2017) Chemical risk assessment and translation to socio-economic assessments. OECD Environment Working Papers. 2017 March 14; (117). http://dx.doi.org/10.1787/a930054b-en
- Chiu et al. (2018) Beyond the RfD: Broad Application of a Probabilistic Approach to Improve Chemical Dose-Response Assessments for Noncancer Effect. EHP, DOI: https://doi.org/10.1289/EHP3368
- Fantke et al. (2018) Advancements in Life Cycle Human Exposure and Toxicity Characterization. EHP, DOI: https://doi.org/10.1289/EHP3871
- Wignall et al. (2018) Conditional Toxicity Value (CTV) Predictor: An In Silico Approach for Generating Quantitative Risk Estimates for Chemicals. EHP, DOI: https://doi.org/10.1289/EHP2998



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